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Early gastric cancer: Treatment, natural history, and prognosis

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INTRODUCTION

Early gastric cancer (EGC) is defined as invasive gastric cancer that invades no more deeply than the submucosa, irrespective of lymph node metastasis (T1, any N). While EGC is of particular importance for patient care in Eastern Asia, its significance extends to other disciplines and patient populations. Early gastric cancer has driven the development of novel imaging technologies (eg, magnification chromoendoscopy and narrow-band imaging) as well as advanced endoscopic resection techniques (eg, endoscopic mucosal resection and endoscopic submucosal dissection). (See "[Chromoendoscopy](#)" and "[Magnification endoscopy](#)", section on '[Stomach](#)' and "[Overview of endoscopic resection of gastrointestinal tumors](#)".)

This topic will review the treatment as well as the natural history and prognosis of early gastric cancer. The clinical manifestations, diagnosis, and staging of early gastric cancer, management of patients with advanced gastric cancer, and management of gastric intestinal metaplasia are discussed elsewhere. (See "[Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging](#)" and "[Initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer](#)" and "[Surgical management of invasive gastric cancer](#)" and "[Local palliation for advanced gastric cancer](#)" and "[Gastric intestinal metaplasia](#)".)

TREATMENT

Overview — Treatment modalities for early gastric cancer (EGC) include endoscopic resection, surgery (gastrectomy), antibiotic treatment for eradication of *Helicobacter pylori*, and adjuvant therapies. Endoscopic resection, by either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), is an option for carefully selected patients who meet specific criteria (ie, have a sufficiently low risk for nodal metastases such that endoscopic resection alone is likely to be curative). The general indications for endoscopic resection are a mucosal tumor without ulceration, ≤ 20 mm in diameter, differentiated histology, and without known lymphovascular invasion. Patients who do not meet the criteria are referred for gastrectomy (which includes resection of the regional nodes), which is discussed elsewhere (see "[Surgical management of invasive gastric cancer](#)", section on 'Extent of lymph node dissection').

Proper staging is crucial for determining which patients are potential candidates for endoscopic resection. The staging of early gastric cancer, including the evaluation of regional lymph nodes for metastatic disease, is discussed in detail elsewhere. (See "[Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging](#)", section on 'Staging'.)

All patients, regardless of approach, should be evaluated for *H. pylori* infection and treated if there is evidence of infection. (See "[Helicobacter pylori infection](#)" below.)

Adjuvant therapy is generally recommended for those patients with stage II or higher ([table 1](#)) gastric cancer following gastrectomy. (See "[Adjuvant therapies](#)" below.)

Endoscopic therapies — For patients without suspected lymph node involvement who meet the standard criteria for endoscopic resection (a mucosal tumor without ulceration, size ≤ 20 mm in diameter, differentiated histology, and without known lymphovascular invasion), endoscopic resection is the preferred approach, rather than gastrectomy, provided that there is local expertise in endoscopic resection techniques. ESD is emerging as the preferred endoscopic technique in Asia and in Western centers with expertise because it achieves a deeper resection margin and allows for en bloc resection. EMR may be performed for removing selected lesions (eg, size < 10 mm) [1]. (See "[ESD versus EMR](#)" below.)

There are no randomized trials comparing endoscopic versus surgical management of early gastric cancer. The data comparing outcomes in patients treated with endoscopic resection by EMR with those treated with gastrectomy suggest similar clinical outcomes [2,3]. In a matched cohort study, there were no differences between the treatments with regard to mortality, recurrence rates, or complications [2]. Patients treated with EMR had a higher risk of metachronous gastric cancers, though all were successfully treated. Patients in the EMR group had shorter median hospital stays (8 versus 15 days) and lower costs of care.

Standard and expanded criteria for endoscopic resection — General guidelines for selecting patients with early gastric cancer who are appropriate for curative endoscopic resection are primarily based upon the risk of lymph node metastases observed in surgical resections [4-7]:

- High probability of en bloc resection
- Tumor histology
 - Differentiated adenocarcinoma
 - Tumor confined to the mucosa
 - Absence of venous or lymphatic invasion
- Tumor size and morphology
 - ≤ 20 mm in diameter, without ulceration

Expansion of the criteria was proposed by centers in Eastern Asia [5,8-10]. In our view, use of expanded criteria for curative endoscopic management should remain investigational, be limited to the following categories, and restricted to centers of excellence [11]:

- Mucosal tumors of any size, differentiated type and without ulceration
- Mucosal tumors less than 30 mm in size, differentiated type, with ulceration
- Mucosal tumors 20 mm in size or smaller, undifferentiated type, without ulceration
- Submucosal tumors less than 30 mm confined to the upper 0.5 mm of the submucosa without lymphovascular invasion

Patients meeting the expanded criteria are at lower risk of lymph node metastases compared with patients who do not meet them. However, patients meeting expanded criteria are at an increased risk of lymph node metastases compared with those who meet standard criteria, but rates are still low (0.2 versus 0.7 percent in a systematic review) [12]. In addition, endoscopic resection may also serve as an excisional biopsy for improved staging. (See '[Endoscopic submucosal dissection](#)' below and "[Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging](#)", section on '[Lymph node metastases in EGC](#)').)

Endoscopic mucosal resection

Initial treatment — Studies have shown high survival and cure rates in patients with early gastric cancer who undergo EMR. In a Japanese report of 131 patients with differentiated mucosal early gastric cancer less than 2 cm, the 5- and 10-year overall survival rates were 84 and 64 percent, respectively. The disease-specific survival rates at both 5- and 10-year follow-up

were 99 percent [13]. In one of the larger series from Europe that included 39 patients with small tumors at low risk of recurrence, 97 percent of patients achieved remission after initial treatment [14]. However, recurrent or metachronous lesions developed in 11 patients (29 percent) during a mean of 57 months of follow-up, yet all were treated successfully with repeat endoscopic therapy.

Complications of EMR include bleeding and perforation, though in experienced hands, EMR is a safe procedure that can be performed on outpatients. (See "[Overview of endoscopic resection of gastrointestinal tumors](#)", section on 'Adverse events'.)

Positive margins — Not all patients with tumor-positive resection margins after EMR will have residual tumor or tumor recurrence. The best way to manage patients with only positive lateral margins is controversial, although case series suggest that patients with positive lateral margins but without positive vertical margins, submucosal invasion, or lymphovascular invasion can be managed with further endoscopic therapy rather than surgery. Patients with positive vertical margins, submucosal invasion, and/or lymphovascular invasion, are generally referred for surgery, depending upon comorbidities and patient wishes.

In a study of 726 Japanese patients treated by EMR, 348 (48 percent) had incomplete resections, 309 (89 percent) of whom had only positive lateral margins [15]. Of these 309 patients, 288 (93 percent) were followed endoscopically (with or without additional endoscopic treatment) with no recurrences. Among the remaining 21 patients who underwent gastrectomy, none had positive lymph nodes. Of the 39 patients in the higher-risk group (positive vertical margins or submucosal/lymphovascular invasion), 24 underwent gastrectomy. In this group, four patients (17 percent) had positive lymph nodes at surgery. In a study of 102 Korean patients with positive lateral or vertical resection margins, residual tumor was detected in 17 of 46 (37 percent) of those who underwent immediate additional endoscopic or surgical resection; tumor recurrence was seen in 17 of 56 (30 percent) who did not undergo immediate therapy but were followed endoscopically [16]. On multivariable analysis, the only independent risk factor for residual tumor/tumor recurrence was the length of the lateral resection margin with tumor involvement.

Assessing the completeness of resection is more difficult in patients who have their tumors removed piecemeal compared with those who have an en bloc resection, and patients undergoing piecemeal resection are at increased risk of recurrence. In a 10-year follow-up study of 149 patients with early gastric cancer who underwent EMR in Japan, the tumors were removed en bloc in 66 cases and piecemeal in 83 [17]. None of the patients with an en bloc resection had a recurrence. Of the patients with piecemeal resections, nine (11 percent) underwent surgery for positive margins. Recurrences were noted in 21 of the 74 patients (28 percent) who did not undergo surgery following piecemeal resection and were more common

among those with unclear lateral margins (adjusted hazard ratio 1.6; 95% CI 1.1-2.4). The recurrences were treated with surgery (eight patients) or with additional endoscopic therapy (13 patients). Despite the 28 percent recurrence rate in patients who underwent piecemeal resection, there were no deaths due to gastric cancer during the 10-year follow-up period.

Endoscopic submucosal dissection — ESD is a specialized endoscopic resection technique that uses a modified needle knife to remove the lesion by dissecting through the submucosa; it offers the potential to remove mucosal and submucosal tumors en bloc (ie, in one piece) irrespective of size of the lesion. ESD is an emerging approach for treatment of early gastric cancer, and most experience is found in specialized centers in eastern Asia [18].

Initial treatment — ESD permits en bloc resection of larger tumors than can be treated with EMR [19-26]. As noted above, larger tumors are at higher risk of requiring piecemeal resection with EMR, which is associated with higher recurrence rates. ESD also permits a deeper resection margin in patients with submucosal involvement who are candidates for endoscopic resection. ESD has also been combined with laparoscopic sentinel lymph dissection [27,28]. (See ['Standard and expanded criteria for endoscopic resection'](#) above and ["Overview of endoscopic resection of gastrointestinal tumors"](#).)

ESD involves a five step process: marking, injection, incision, dissection, and en bloc retrieval. Various types of endoscopic electrosurgical needle knives are used to incise mucosa surrounding the tumor. The mucosa is subsequently dissected away from the underlying submucosa, and the entire tumor is removed en bloc. ESD is more technically challenging than EMR and, for the most part, ESD is performed in high-volume referral centers. English-language publications that included >300 ESD cases suggest that major complications include: perforation (1 to 5 percent), delayed perforation (0.5 percent), delayed bleeding (3.6 to 16 percent), stenosis (0.7 to 2 percent overall, with rates up to 17 and 7 percent for cardia and peripyloric resections, respectively), and aspiration pneumonia (0.8 to 2 percent) [29-35].

ESD versus EMR — While ESD requires more procedure time, endoscopic skill and expertise (in addition to posing greater risk compared with EMR), ESD is more likely to result in complete resection of early gastric cancer [36].

In a meta-analysis of 10 observational studies including over 4300 lesions, patients treated with ESD were more likely to have en bloc resection or complete histologic resection compared with patients treated with EMR (OR 9.7, 95% CI 7.7-12.1 and OR 5.7, 95% CI 2.9-11.0, respectively) [36]. The likelihood of local recurrence was lower in patients treated with ESD compared with EMR (OR 0.09, 95% CI 0.05-0.17). The risk of perforation was higher in patients treated with ESD

compared with EMR (OR 4.7, 95% CI 2.8-7.9), while the risk of bleeding was not significantly different between the two groups.

Expertise and experience in ESD continues to expand in centers outside of Asia [37-39], with support from some guidelines for ESD as the preferred endoscopic treatment of early superficial gastric tumors [40,41]. In a North American cohort study including 139 patients with early gastric cancer who were managed with ESD, en bloc resection was accomplished in 130 (94 percent) [42]. Estimates of the learning curve for ESD among advanced endoscopists in the United States are emerging [43]. ESD is regarded as the treatment of choice in the European and British guidelines for the management of early gastric neoplasia [40,41]. The British guidelines include ESD as an option for gastric low-grade dysplasia with visible mucosal irregularities, to augment the sensitivity of the sampling to detect EGC.

Positive margins — Some studies suggest that gastrectomy should be considered for patients who are surgical candidates and who have residual cancer present at the lateral or vertical resection margins following ESD. This was illustrated in a study that examined 118 patients who underwent gastrectomy following incomplete ESD [44]. ESD was considered incomplete if there was residual cancer at the ESD margin, invasion of the submucosa or muscularis propria by tumor, lymphatic invasion, or an undifferentiated cell type. A total of 27 patients (23 percent) had residual cancer at the ESD margin, and 29 patients (25 percent) had residual cancer in the gastrectomy specimen. Patients with a tumor present at the lateral margin of the ESD specimen had a particularly high rate of residual tumor (63 percent, hazard ratio 13; 95% CI 3.8-44).

On the other hand, good outcomes among patients with positive lateral margins (but without other criteria for an incomplete resection) have been seen when they are followed with close observation, rather than gastrectomy. In a series of 77 patients who had positive lateral margins following ESD who were followed closely after ESD, locally recurrent cancer was found in 10 patients (13 percent) after a median follow-up of 60 months [45]. On multivariable analysis, a positive lateral margin ≥ 6 mm was associated with an increased risk of recurrence (hazard ratio 21; 95% CI 5.2-83 percent). Eight patients were managed with ESD and two underwent gastrectomy. There were no deaths due to gastric cancer, and the overall five-year survival rate was 94 percent.

Managing noncurative resection — In addition to positive margins, there are other definitions of a noncurative endoscopic resection, including submucosal involvement, lymphovascular invasion, and poorly differentiated histology. The goal of endoscopic therapy is en bloc resection, but noncurative resection remains a challenge and there is no standard approach for managing these patients. Any endoscopic resection that does not meet the

expanded criteria is a noncurative resection and typically, gastrectomy has been recommended, especially for tumors with positive vertical margins and/or with submucosal involvement or lymphovascular invasion, which are associated with a higher risk for lymph node metastases. (See '[Standard and expanded criteria for endoscopic resection](#)' above.)

However, some patients with noncurative resection are not good surgical candidates or wish to avoid further invasive intervention. Risk factors that predict lymph node metastasis have been identified that may help treatment decisions in these patients. In a study of 321 patients who had gastrectomy and lymph node dissection after noncurative endoscopic resection for early gastric cancer, 23 (7 percent) of patients had lymph node metastasis (LNM) [46]. Risk factors associated with LNM included lymphovascular invasion (OR 8.7, 95% CI 2.9-26.8), positive vertical margins (OR 3.8, 95% CI 1.4-9.8) and female sex (OR 2.5, 95% CI 1.0-6.1) [46]. Despite these data, additional treatment may provide few benefits to patients who do not have a long life expectancy. In a single center study of 159 patients who underwent noncurative endoscopic resection but without additional treatment, three- and five-year survival rates were 83 and 77 percent, respectively, although rates were lower for those with lymphovascular invasion (62 and 42 percent, respectively) [47].

Among patients undergoing gastrectomy, studies have looked at performing laparoscopic lymph node dissection in patients with negative margins after ESD but noncurative resection based upon other factors (eg, undifferentiated histology, presence of lymphovascular or submucosal invasion). Currently, gastrectomy with removal of perigastric lymph nodes is recommended for such patients, but small studies suggest that laparoscopic lymph node dissection without gastrectomy may be a reasonable alternative. In a study of 21 patients with negative margins but with risk factor for lymph node metastases, lymph node dissection revealed metastases in two patients (10 percent) [48]. The patients with lymph node metastases were offered gastrectomy, but declined additional treatment. There were no local recurrences in any of the 21 patients during a median follow-up of 61 months, though two patients developed metachronous early gastric cancers and were again treated with ESD.

Other endoscopic modalities — Other endoscopic modalities have been investigated but do not have an established role in the treatment of early gastric cancer. These include photodynamic therapy [49-51], Nd:YAG laser treatment [52-54], and argon plasma coagulation [55,56]. (See "[Basic principles of medical lasers](#)", section on '[Solid state](#)' and "[Argon plasma coagulation in the management of gastrointestinal hemorrhage](#)", section on '[Principles and equipment](#)'.)

In one study, 27 patients with early gastric cancer were treated with the photosensitizer [porfimer](#) (Photofrin II). Their tumors were then exposed to an argon laser [49]. A complete

response to therapy was observed in 88 percent. An important caveat is that these therapies are considered "tissue-destroying" therapies, without available pathology specimens for examination, whereas EMR and ESD are "tissue-retrieving" therapies [19].

Gastrectomy — We recommend that gastrectomy should be performed for patients with lymph node involvement detected or highly suspected during preoperative staging to remove both the tumor and the lymph nodes. Gastrectomy permits the evaluation and removal of involved lymph nodes, which is important because lymph node metastases are associated with tumor recurrence. (See "[Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging](#)", section on 'Staging work-up'.)

Other indications for gastrectomy rather than endoscopic resection are (see '[Standard and expanded criteria for endoscopic resection](#)' above):

- Low probability of a successful en bloc endoscopic resection (ie, lesion requires piecemeal resection)
- Mucosa-limited tumor with undifferentiated (poorly differentiated or signet ring adenocarcinoma) rather than differentiated type adenocarcinoma
- Submucosal tumor of any size, any histology
- Evidence of lymphovascular (lymphatic or venous) invasion in the primary tumor
- Positive margins after EMR or ESD
- If requirements for endoscopic resection are met but providers with appropriate endoscopic expertise are not available

Although endoscopic resection can be used for the treatment of patients meeting appropriate criteria in countries with a high incidence of early gastric cancer and appropriate resources, gastrectomy remains the most widely used approach worldwide for the treatment of early gastric cancer. Gastrectomy is associated with overall five-year survival rates of up to 98 percent [57-63].

Larger tumor size, a penetrating growth pattern, undifferentiated histology, and positive lymph nodes are all associated with worse prognosis for patients following gastrectomy. This was illustrated in an Italian series of over 1000 patients with EGC who underwent either subtotal or total gastrectomy with D2 lymphadenectomy, in whom the cancer-specific mortality rate at five years was 6 percent (95% CI 5 to 8 percent) [63]. The mortality risk was higher for patients with lesions >2 cm (adjusted HR 1.44, 95% CI 1.07-1.94), Pen A-type disease (ie, a tumor with

expansively penetrating growth pattern [64]) (adjusted HR 1.73, 95% CI 1.15-2.61), and nodal positivity (adjusted HR 2.28, 95% CI 1.61-3.21).

The basic principles underlying the performance of surgery (ie, total versus subtotal, extent of lymph node dissection, laparoscopic versus open surgery) are the same as those that apply to more advanced gastric cancers. (See "[Surgical management of invasive gastric cancer](#)".)

In general:

- Either subtotal or total gastrectomy is performed, depending upon the tumor location [65-72]. A total gastrectomy is usually performed for lesions in the upper third of the stomach, and subtotal gastrectomy for lesions in the lower two-thirds [65]. (See "[Surgical management of invasive gastric cancer](#)".)
- Laparoscopic surgery may represent a technically feasible alternative to open gastrectomy when it is performed in experienced centers. Multiple randomized trials and a meta-analysis of five of the trials and 17 nonrandomized comparisons of laparoscopic versus open gastrectomy for early gastric cancer have concluded that laparoscopic surgery reduces intraoperative blood loss, postoperative pain, length of hospital stay, and postoperative morbidities, while recovering a similar number of lymph nodes compared with open surgery. However, additional data from methodologically high-quality comparative trials with long-term follow-up are needed before it can be confidently concluded that oncologic outcomes are comparable to those obtained by open gastrectomy. (See "[Surgical management of invasive gastric cancer](#)", section on '[Open versus laparoscopic resection](#)'.)

The role of adjuvant therapy following gastrectomy is addressed below (see '[Adjuvant therapies](#)' below).

Helicobacter pylori infection — We recommend *Helicobacter pylori* (*H. pylori*) eradication therapy for patients with early gastric cancer who are found to be infected. Treatment is important because *H. pylori* infection is a well-defined risk factor for both early and invasive gastric cancer. In addition, *H. pylori* infection is associated with the development of metachronous gastric cancers, and eradication decreases the risk of developing metachronous gastric cancer after treatment of early gastric cancer.

H. pylori organism loads may decrease with the onset of precancerous lesions and adenocarcinoma, thereby reducing biopsy sensitivity. In the event of negative biopsies for *H. pylori*, infection status should be determined with serology. Any patient with positive serology who does not have a definitive history of having been treated for *H. pylori* should receive

treatment, even if biopsies are negative. (See ["Indications and diagnostic tests for Helicobacter pylori infection in adults"](#) and ["Treatment regimens for Helicobacter pylori in adults"](#) and ["Association between Helicobacter pylori infection and gastrointestinal malignancy"](#).)

H. pylori infection is a well-defined risk factor for gastric cancer. (See ["Gastric cancer: Pathology and molecular pathogenesis"](#), section on '[Helicobacter pylori](#)'.)

Some studies, including two randomized trials, have found that eradication of *H. pylori* decreases the risk of developing metachronous dysplasia or cancer following treatment of early gastric cancer [73-76], but others have not [77,78].

This issue was addressed in a systematic review and meta-analysis that included two randomized trials [75,77] and eight cohort studies including patients with EGC who were treated with endoscopic resection [79]. After adjusting for baseline gastric cancer incidence, patients with eradication of *H. pylori* infection after endoscopic resection had lower incidence of metachronous gastric cancer compared with those who did not receive eradication therapy (incidence rate ratio [IRR] 0.46, 95% CI 0.35-0.60) [79]. This result compared favorably to the benefit of eradication in asymptomatic infected individuals without a prior history of EGC (IRR 0.62, 95% CI 0.49-0.79).

A similar magnitude of protective benefit was shown in a later placebo-controlled randomized trial of eradication therapy in 470 patients following endoscopic resection of EGC or high-grade adenoma (hazard ratio [HR] for metachronous cancer in the treatment group 0.50; 95% CI 0.26 to 0.94) [74].

In several regions of high gastric cancer incidence, routine screening and eradication for *H. pylori* has been implemented or is being evaluated to decrease rates of gastric cancer [80]. There are limited data that suggest that screening for *H. pylori* in asymptomatic healthy individuals in areas of high gastric cancer incidence may decrease the risk of gastric cancer [81-84]. Successful eradication of *H. pylori* infection in first-degree relatives with gastric cancer has been demonstrated to significantly reduce the risk of a subsequent gastric cancer in areas of high cancer incidence [85]. This subject is discussed elsewhere. (See ["Gastric cancer screening"](#), section on '[Helicobacter pylori eradication](#)'.)

Adjuvant therapies — The role of adjuvant therapy, either with systemic chemotherapy or radiotherapy or both for patients who have undergone complete endoscopic resection of early gastric cancer (T1a or b) is not clearly established, and it is generally not recommended. The 2017 consensus-based guidelines for management of gastric cancer from the National Comprehensive Cancer Network [86,87], as well as guidelines from ESMO [7] and Japan [5] all

recommend observation without adjuvant therapy for patients with Tis or T1, N0 disease ([table 1](#)) who have uninvolved resection margins.

On the other hand, adjuvant chemotherapy is generally recommended for all patients with node-positive or T3N0 ([table 1](#)) gastric cancer following gastrectomy [5,7], although this recommendation has been challenged for patients with resected early gastric cancer with no more than one or two lymph node metastases (ie, T1N1 tumors) [88,89]. The benefit of adjuvant therapy for resected T2N0 gastric cancer is debated. A general discussion of adjuvant therapy for resected gastric cancer is presented in more detail elsewhere (see "[Adjuvant and neoadjuvant treatment of gastric cancer](#)", section on 'Initial potentially curative resection').

NATURAL HISTORY AND PROGNOSIS

Prognosis without treatment — An early report from Japan suggested that without treatment, 63 percent of patients with early gastric cancer will progress to advanced stage disease within five years (6 to 88 months) [90]. Early gastric cancer may represent a meta-stable biologic state, with doubling times on the order of several years, versus advanced cancer with doubling times of less than a year [90,91].

Prognosis following treatment — The overall five-year survival rate for treated early gastric cancer in most modern era series is over 90 percent: nearly 100 percent for mucosal tumors, and 80 to 90 percent for submucosal tumors [92-95]. Survival rates are similar between patients who undergo endoscopic resection and those who undergo surgical resection (five-year survival of 96 and 94 percent in one study) [96-98]. The recurrence rate after surgery is approximately 1 to 5 percent in reports from Korea [96,99] and Japan [100] and 5 to 15 percent in studies from Western centers [101]. These variable recurrence rates partially reflect differences in length of follow-up, but may also be due to differences in the pathologic diagnosis of malignancy [102]. Among patients undergoing endoscopic resection, recurrence rates have been reported to be between 0 and 30 percent [16,17,21,29,37,96,100,103,104]. Higher recurrence rates are seen with those who have piecemeal or incomplete resections. (See '[Endoscopic therapies](#)' above and '[Gastrectomy](#)' above and "[Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging](#)", section on 'Histologic classification'.)

Synchronous and metachronous gastric cancers are common in patients with early gastric cancer [66,105-109]. In a Japanese series, 58 of 633 patients (9.2 percent) with early gastric cancers had synchronous cancers, defined as a second cancer found within the first year [110]. In long-term follow-up, the overall incidence of metachronous cancers was 8.2 percent, the majority of which were able to be resected endoscopically. This was echoed in a Korean

retrospective study of 602 patients treated with ESD over 4.5 years, wherein 2 percent had synchronous advanced gastric lesions (seven adenocarcinomas, five adenomas with dysplasia) that were not detected during the initial evaluation, underscoring the importance of careful endoscopic inspection [105]. In another Japanese study with 1526 patients who were followed long-term, the cumulative incidence of metachronous early gastric cancers was 9.5 percent at five years, 13.1 percent at seven years, and 22.7 percent at 10 years [108]. In patients who have undergone partial gastrectomy, late recurrences or metachronous lesions occur in the gastric remnant in approximately 2 to 8 percent of cases of early gastric cancer [66,106,107].

Factors that have been associated with metachronous gastric dysplasia and cancer following ESD include failure to eradicate *H. pylori* and age ≥ 60 years [73,111].

Prognosis with lymph node involvement — The literature suggests that up to 10 percent of mucosal early gastric cancers and 20 to 30 percent of submucosal early gastric cancers will have lymph node metastases [6,112-115].

The prognostic importance of lymph node involvement in early gastric cancer has been illustrated in several studies of patients who have undergone gastrectomy [71,106,116,117]:

- In a Korean study, long-term survival was 95 percent in patients with no lymph node involvement, 88 percent in those with one to three nodes involved, and 77 percent in those with more than three nodes involved [71].
- A large retrospective multicenter Italian study in patients with early gastric cancer reported long-term survival after surgical resection of 92, 82, 73, and 27 percent for patients with 0, 1 to 3, 4 to 6, and >6 positive nodes, respectively [116].
- Another series retrospectively evaluated 621 patients with early gastric cancer who underwent gastrectomy with lymphadenectomy [106]. Lymph node metastases were observed in 10 percent of cases, and the median follow-up was 123 months. Recurrence during follow-up was much lower in those without nodal involvement (1.8 versus 9.5 percent). As in other studies, the risk of lymph node metastasis increased significantly with submucosal invasion and greater tumor size [106,118,119].

POST-TREATMENT SURVEILLANCE

There are no randomized trials to guide surveillance strategies following remission from early gastric cancer. We follow consensus-based guidelines from the National Comprehensive Cancer Network [86,87], which suggest a risk-stratified posttreatment surveillance as follows:

For resected Tis disease treated by endoscopic resection:

- History and physical examination every three to six months for years 1 to 2, every 6 to 12 months for years 3 to 5, and then annually
- Complete blood count and chemistry profile as indicated
- EGD every six months for one year, then annually for three years
- Radiologic imaging as clinically indicated based on symptoms and concern for recurrence

For T1a/T1b disease treated by gastrectomy or T1a disease treated by endoscopic resection:

- History and physical examination every three to six months for years 1 to 2, every 6 to 12 months for years 3 to 5, and then annually
- Complete blood count and chemistry profile as indicated
- For patients treated by endoscopic resection, EGD every six months for one year, then annually up to five years; for patients treated by surgical resection, EGD as clinically indicated.
- CT chest, abdomen, and pelvis as clinically indicated as clinically indicated based on symptoms and concern for recurrence
- Monitor for nutritional deficiency in surgically resected patients and treat as indicated

For pathologic stage II disease treated by gastrectomy:

- History and physical examination every three to six months for years 1 to 2, every 6 to 12 months for years 3 to 5, and then annually
- Complete blood count and chemistry profile as indicated
- EGD as clinically indicated.
- CT chest, abdomen, and pelvis every 6 to 12 months for first two years, then annually up to five years.
- Monitor for nutritional deficiency in surgically resected patients and treat as indicated

Guidelines for posttreatment surveillance from ESMO also recommend tailoring the surveillance strategy to the individual patients and the stage of disease, but provide no specific guidance for those with early gastric cancer [7].

It should be noted that performing endoscopy sooner than three months following resection is of limited benefit [120]. The exact surveillance interval needs to be defined with randomized trials. A retrospective study conducted in Korea suggests that there is no difference in outcomes for subjects screened at one-, two-, or three-year intervals [121]. In addition, the routine use of computed tomography as a component of post-treatment surveillance does not appear to be of benefit [122].

Surveillance endoscopies permit endoscopic treatment of cancers that may have been missed during the initial endoscopic resection or that subsequently developed. The use of routine surveillance endoscopy is supported by a multicenter retrospective cohort study from Japan [123]. The study included 1258 patients who underwent endoscopic submucosal dissection (ESD) for early gastric cancer. Following ESD, patients underwent surveillance endoscopy every 6 to 12 months. During a median follow-up of 27 months, synchronous (occurring within one year of ESD) or metachronous (after one year) cancers were detected in 175 patients (14 percent), and local recurrence was detected in five patients (0.4 percent). One hundred sixty-four of the synchronous and metachronous cancers (94 percent) were successfully treated with repeat ESD.

TREATMENT OF METACHRONOUS GASTRIC CANCER

As with the original tumor, metachronous early gastric cancers may be treated with surgery or endoscopic therapy, depending on the tumor characteristics and local expertise. The performance of a prior partial gastrectomy does not preclude the use of endoscopic therapy in appropriately selected patients. (See ['Standard and expanded criteria for endoscopic resection'](#) above.)

The diagnosis of a metachronous gastric cancer versus recurrence may be difficult, but a different histologic type compared with the original tumor and location that is non-anastomotic favors a metachronous cancer in the gastric remnant. Results of surgical resection may be more favorable when a gastric remnant adenocarcinoma develops at a non-anastomotic site. As an example, in a series of 128 patients who developed an early metachronous gastric cancer in the gastric remnant following partial gastrectomy, curative resections were achieved for 109 lesions, with overall and disease-specific five-year survival rates of 87 and 100 percent [124].

For tumors that invade beyond the submucosa, treatment options include surgery or radiation therapy with or without concurrent chemotherapy. (See ["Surgical management of invasive gastric cancer"](#), section on ['Gastric remnant carcinoma'](#) and ["Local palliation for advanced gastric cancer"](#).)

TREATMENT OF RECURRENCE

The treatment options in patients who develop recurrent early gastric cancer include surgery and repeat attempts at endoscopic resection (typically endoscopic submucosal dissection). There are no clear guidelines on which patients with recurrent early gastric cancer should be considered for endoscopic treatment. Our approach is to perform an endoscopic ultrasound to

assess the depth of invasion and then attempt repeat endoscopic therapy in patients who meet standard criteria for endoscopic resection. For other patients, we suggest surgical resection. (See ['Standard and expanded criteria for endoscopic resection'](#) above.)

Studies suggest that appropriately selected patients who undergo endoscopic resection have good results [125-127]. In a series of 95 patients with tumor recurrence following endoscopic resection (EMR in 75 cases, ESD in 20 cases), repeat endoscopic resection was curative in 81 percent [125]. There were no further recurrences among the 77 patients who underwent a complete, potentially curative resection. Although the report does not indicate how patients were chosen for endoscopic resection, the vast majority had disease limited to the mucosa (96 percent) and had no evidence of lymphovascular invasion (99 percent).

Local treatment options for patients with recurrent gastric cancer that invades beyond the submucosa include surgery or radiation therapy with or without concurrent chemotherapy. (See ["Surgical management of invasive gastric cancer"](#) and ["Local palliation for advanced gastric cancer"](#).)

SPECIAL CONSIDERATIONS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has increased the complexity of cancer care. Important issues include balancing the risk from delaying diagnostic evaluation and cancer treatment versus harm from COVID-19, minimizing the number of clinic and hospital visits to reduce exposure whenever possible, mitigating the negative impacts of social distancing on delivery of care, and appropriately and fairly allocating limited healthcare resources. Given that upper endoscopy procedures are considered high risk due to exposure to potentially infected aerosolized upper respiratory secretions, many hospitals and outpatient facilities are postponing or canceling these procedures until the pandemic abates. Specific guidance for decision-making for upper gastrointestinal cancers is available from the [Society for Surgical Oncology](#), [European Society for Medical Oncology](#), and others. General recommendations for cancer care during active phases of the COVID-19 pandemic are discussed separately. (See ["COVID-19: Considerations in patients with cancer"](#).)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See ["Society guideline links: Gastric cancer"](#).)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "[Patient education: Stomach cancer \(The Basics\)](#)")

SUMMARY AND RECOMMENDATIONS

- Early gastric cancer is defined as adenocarcinoma limited to the gastric mucosa or submucosa, regardless of involvement of the regional lymph nodes (T1, any N). (See "[Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging](#)", section on 'Introduction'.)
- We recommend that patients with known or suspected lymph node metastases be referred for gastrectomy rather than endoscopic resection (**Grade 1B**). Gastrectomy with removal of perigastric lymph nodes permits the evaluation and removal of involved lymph nodes, which is indicated because lymph node metastases are associated with tumor recurrence. (See 'Gastrectomy' above and '[Prognosis with lymph node involvement](#)' above and "[Early gastric cancer: Epidemiology, clinical manifestations, diagnosis, and staging](#)".)
- For patients without suspected lymph node involvement who meet the standard criteria for endoscopic resection, we suggest endoscopic resection rather than gastrectomy, provided that there is local expertise in the endoscopic resection techniques (**Grade 2C**). The indication for endoscopic resection is a mucosal tumor without ulceration, size ≤ 20 mm in diameter, differentiated histology, and without known lymphovascular invasion. In our view, the use of expanded criteria for endoscopic management remains

investigational and is limited to centers of excellence. (See '[Standard and expanded criteria for endoscopic resection](#)' above.)

Endoscopic resection is associated with less treatment-related morbidity than gastrectomy and data suggest similar outcomes for appropriately selected patients with early gastric cancer.

- For curative endoscopic resection for early gastric cancer, endoscopic submucosal dissection is emerging as the preferred approach in Asia and in Western centers with expertise because it achieves a deeper resection margin and allows for en bloc resection. Endoscopic mucosal resection may be performed for selected lesions (eg, size <10 mm). (See '[Endoscopic therapies](#)' above.)
- For patients with early gastric cancer who have an incomplete endoscopic resection with positive vertical margins, piecemeal endoscopic resection, lymphovascular invasion, or submucosal involvement not meeting the expanded criteria for endoscopic resection, we recommend gastrectomy rather than repeat endoscopic resection (**Grade 1B**). Patients with incomplete resections and only positive lateral margins may be considered for repeat endoscopic resection if there is no evidence of positive vertical margins, lymphovascular invasion, or submucosal involvement. (See '[Endoscopic submucosal dissection](#)' above and '[Endoscopic mucosal resection](#)' above.)
- We recommend gastrectomy for patients with early gastric cancer who do not meet standard or expanded criteria for endoscopic resection (**Grade 1B**). Patients who do not meet criteria for endoscopic resection are at increased risk for lymph node metastases, which are associated with tumor recurrence. Gastrectomy with removal of perigastric lymph nodes permits the evaluation and removal of involved lymph nodes. (See '[Standard and expanded criteria for endoscopic resection](#)' above.)
- Laparoscopic gastrectomy is feasible and safe when conducted by surgeons experienced with the technique. Although this approach is clearly associated with a reduction in morbidity compared with open gastrectomy, additional data from high-quality comparative trials with long-term follow-up are needed before it can be confidently concluded that oncologic outcomes are comparable. (See '[Gastrectomy](#)' above.)
- We recommend *Helicobacter pylori* (*H. pylori*) eradication therapy for patients with early gastric cancer who are found to be infected (**Grade 1B**). Treatment is indicated because *H. pylori* infection is associated with the development of metachronous gastric cancers, and eradication decreases the risk of developing metachronous gastric cancer after treatment of early gastric cancer. In the event of negative biopsies for *H. pylori*, infection status

should be determined with serology, since organism loads decrease in the setting of metaplasia and cancer. Any patient with positive serology who does not have a definitive history of having been treated for *H. pylori* should receive treatment, even if biopsies are negative. (See '[Helicobacter pylori infection](#)' above and "[Association between Helicobacter pylori infection and gastrointestinal malignancy](#)".)

- Adjuvant chemotherapy is generally recommended for all patients with node-positive and/or T2 or higher ([table 1](#)) gastric cancer following gastrectomy. A role for adjuvant chemotherapy in patients who have undergone complete endoscopic resection of a T1 gastric cancer is not clearly established, and it is generally not recommended. (See '[Adjuvant therapies](#)' above.)

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Topic 16858 Version 46.0

GRAPHICS

Stomach cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i> : Intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria*
T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures [¶] ^Δ
T4	Tumor invades the serosa (visceral peritoneum) or adjacent structures [¶] ^Δ
T4a	Tumor invades the serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
<p>* A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.</p> <p>¶ The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.</p> <p>Δ Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.</p>	
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in 1 or 2 regional lymph nodes
N2	Metastases in 3 to 6 regional lymph nodes
N3	Metastases in 7 or more regional lymph nodes

N3a	Metastases in 7 to 15 regional lymph nodes		
N3b	Metastases in 16 or more regional lymph nodes		
Distant metastasis (M)			
M category	M criteria		
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic stage groups			
Clinical (cTNM)			
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	I
T1	N1, N2, or N3	M0	IIA
T2	N1, N2, or N3	M0	IIA
T3	N0	M0	IIB
T4a	N0	M0	IIB
T3	N1, N2, or N3	M0	III
T4a	N1, N2, or N3	M0	III
T4b	Any N	M0	IVA
Any T	Any N	M1	IVB
Pathological (pTNM)			
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IB
T2	N0	M0	IB
T1	N2	M0	IIA
T2	N1	M0	IIA
T3	N0	M0	IIA
T1	N3a	M0	IIB

T2	N2	M0	IIB
T3	N1	M0	IIB
T4a	N0	M0	IIB
T2	N3a	M0	IIIA
T3	N2	M0	IIIA
T4a	N1	M0	IIIA
T4a	N2	M0	IIIA
T4b	N0	M0	IIIA
T1	N3b	M0	IIIB
T2	N3b	M0	IIIB
T3	N3a	M0	IIIB
T4a	N3a	M0	IIIB
T4b	N1	M0	IIIB
T4b	N2	M0	IIIB
T3	N3b	M0	IIIC
T4a	N3b	M0	IIIC
T4b	N3a	M0	IIIC
T4b	N3b	M0	IIIC
Any T	Any N	M1	IV

Post-neoadjuvant therapy (ypTNM)

When T is...	And N is...	And M is...	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	I
T1	N1	M0	I
T3	N0	M0	II
T2	N1	M0	II
T1	N2	M0	II
T4a	N0	M0	II
T3	N1	M0	II
T2	N2	M0	II
T1	N3	M0	II

T4a	N1	M0	III
T3	N2	M0	III
T2	N3	M0	III
T4b	N0	M0	III
T4b	N1	M0	III
T4a	N2	M0	III
T3	N3	M0	III
T4b	N2	M0	III
T4b	N3	M0	III
T4a	N3	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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